Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial

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Summary

Background Otamixaban is an intravenous direct factor Xa inhibitor. We aimed to assess its efficacy and safety in non-ST-elevation acute coronary syndromes and to identify the optimum dose range for further assessment in a phase 3 study.

Methods In this double-blind, phase 2 trial undertaken in 196 sites in 36 countries, 3241 patients with non-ST-elevation acute coronary syndromes were randomly assigned via a central, telephone-based interactive voice response system to one of five doses of otamixaban (0·08 mg/kg bolus followed by infusions of 0·035 [n=125], 0·070 [676], 0·105 [662], 0·140 [658], or 0·175 [671] mg/kg/h) or to a control of unfractionated heparin (60 IU/kg intravenous bolus followed by an infusion of 12 IU/kg/h) plus eptifibatide (180 µg/kg intravenous bolus followed by an infusion of 1·0–2·0 µg/kg/min [n=449]). Both investigators and patients were unaware of treatment allocation. Enrolment into the lowest dose group was stopped early at the recommendation of the Data Monitoring Committee. The primary efficacy endpoint was a composite of death, myocardial infarction, urgent revascularisation, or bailout glycoprotein IIb/IIIa inhibitor use up to 7 days. The primary safety endpoint was TIMI major or minor bleeding not related to coronary-artery bypass grafting. Efficacy analyses were by intention to treat; safety analyses were in treated patients. This study is registered with ClinicalTrials.gov, number NCT00317395.

Findings Rates of the primary efficacy endpoint in the five otamixaban doses were 7·2% (nine of 125) with 0·035 mg/kg/h, 4·6% (31/676) with 0·070 mg/kg/h, 3·8% (25/662) with 0·105 mg/kg/h, 3·6% (24/658) with 0·140 mg/kg/h, and 4·3% (29/671) with 0·175 mg/kg/h (p=0·34 for trend). In the control group, the rate was 6·2% (28/449), yielding relative risks for the five otamixaban doses of 1·16 (95% CI 0·56–2·38), 0·74 (0·45–1·21), 0·61 (0·36–1·02), 0·58 (0·34–1·00), and 0·69 (0·42–1·15), respectively. Rates of the primary safety endpoint in the five otamixaban doses were 1·6% (two of 122), 1·6% (11/669), 3·1% (20/651), 3·4% (22/651), and 5·4% (36/664), respectively (p=0·0001 for trend); the rate in the control group was 2·7% (12/448).

Interpretation In patients with non-ST-elevation acute coronary syndromes, otamixaban infusions of 0·100–0·140 mg/kg/h might reduce ischaemic events and have a safety profile similar to unfractionated heparin plus eptifibatide. Further testing in a phase 3 trial is warranted.

Funding Sanofi-Aventis.

Lancet 2009; 374: 787–95

Published Online August 30, 2009 DOI:10.1016/S0140-6736(09)61454-9

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Introduction

Acute coronary syndromes are a leading cause of mortality and morbidity worldwide and typically occur when intracoronary thrombus forms at the site of atherosclerotic plaque rupture. Plaque rupture leads to exposure of tissue factor and consequent activation of factor X.[1] Factor Xa is a key component of the prothrombinase complex that drives the final common pathway of the coagulation cascade, generating thrombin, which then converts fibrinogen to insoluble fibrin. Thrombin is also a potent activator of platelets via cleavage and consequent stimulation of the protease-activated receptor (PAR) 1 on the platelet surface.[2] Thus, inhibition of thrombin generation, activity, or both, is a logical aim in the treatment of acute coronary syndromes.

For many years, unfractionated heparin has been the cornerstone of anticoagulant therapy for patients presenting with a non-ST-elevation acute coronary syndrome.[3,4] However, unfractionated heparin has several limitations: it is an indirect, non-selective inhibitor of coagulation factors; it cannot inhibit clot-bound thrombin; it can cause heparin-induced thrombocytopenia; and it has unpredictable pharmacodynamic activity.[5] By contrast, otamixaban is a novel, intravenous, direct, selective inhibitor of factor Xa.[6,7] Otamixaban has an initial half-life of about 30 min and predictable pharmacodynamic activity that, by contrast with unfractionated heparin, obviates the need for anticoagulation monitoring.

In the SEPIA-PCI trial, a dose-ranging phase 2 study of otamixaban compared with unfractionated heparin in

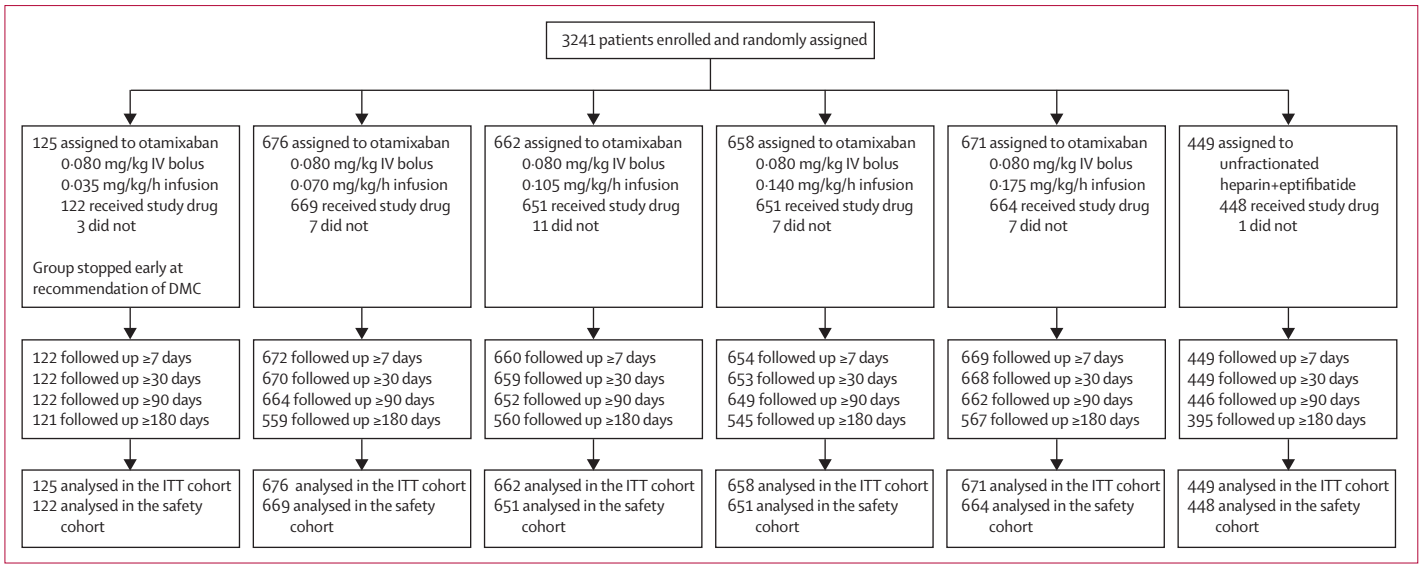

Figure 1: **Trial profile**
We did not keep screening logs in this acute population. IV=intravenous. DMC=Data Monitoring Committee. ITT=intention to treat.

947 patients undergoing non-urgent percutaneous coronary intervention, the highest dose of otamixaban was better than unfractionated heparin in reduction of thrombin generation (as measured with prothrombin fragments 1 and 2).[8] Moreover, although not designed to detect differences in the incidence of clinical events, in patients given intermediate doses of otamixaban (0·120 and 0·160 mg/kg/h), the rates of the clinical composite endpoint of death, myocardial infarction, or the need for urgent target vessel revascularisation tended to be 30–55% lower than was the rate in the unfractionated heparin group, and the rates of TIMI major or minor bleeding were similar.

Encouraged by these promising results, we designed the SEPIA-ACS1 TIMI 42 trial (Study Program to Evaluate the Prevention of Ischemia with direct Anti-Xa inhibition in Acute Coronary Syndromes 1—Thrombolysis in Myocardial Infarction 42) to assess the efficacy and safety of several different doses of otamixaban compared with unfractionated heparin plus eptifibatide in patients with high-risk non-ST-elevation acute coronary syndromes, and to identify the optimum dose range for further assessment in a phase 3 study.

Methods

Study design and participants

In this randomised, double-blind, phase 2, parallel group, dose-ranging, active-controlled clinical trial, 3241 patients were randomly assigned at 196 sites in 36 countries. Patient enrolment took place from June 19, 2006, to Nov 19, 2008. The trial enrolled patients aged 18 years or older who were within 24 h of having symptoms at rest of at least 10 min duration that were suggestive of an acute coronary syndrome; had high-risk features consisting of either new or presumably new ST-segment deviation (depression or transient elevation) of 0·1 mV or greater in two or more contiguous electrocardiograph leads, or a cardiac biomarker of necrosis (cardiac troponin or creatine kinase MB) above the upper limit of normal; and were planned to be treated with an early invasive strategy with coronary angiography.

Major exclusion criteria were treatment with an anticoagulant for the acute coronary syndrome for more than 24 h before randomisation, requirement for treatment with an oral anticoagulant, contraindications to eptifibatide (including bleeding within the previous 30 days or known bleeding diathesis, severe hypertension defined as systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg, major surgery or trauma in the past 6 weeks, history of stroke in the past 30 days or any history of haemorrhagic stroke, or creatinine clearance <30 mL/min or dependence on renal dialysis), a platelet count less than 100 000 per µL of blood, an international normalised ratio of 2 or more, previous percutaneous coronary intervention within 30 days of randomisation, or cardiogenic shock.

The study was approved by the relevant ethics board at every participating site, and all patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned to one of six parallel groups, initially in 1:1:1:1:1:1 ratio, to receive either one of five otamixaban (Sanofi-Aventis, Frankfurt, Germany) regimens (0·08 mg/kg intravenous bolus followed by an infusion of 0·035, 0·070, 0·105, 0·140, or 0·175 mg/kg/h—doses similar but not identical to those studied in SEPIA-PCI[8]) or an active control of unfractionated heparin (Sanofi Winthrop, Notre Dame de Bondeville, France) (60 IU/kg intravenous bolus [maximum 4000 IU], followed by an infusion of

	Otamixaban (mg/kg/h)					UFH+eptifibatide (n=449)
	0·035 (n=125)	0·070 (n=676)	0·105 (n=662)	0·140 (n=658)	0·175 (n=671)	
General characteristics						
Age (years)	60·0 (13·1)	61·6 (11·3)	61·7 (11·3)	61·5 (11·3)	61·3 (11·6)	61·0 (11·5)
Men	92 (73·6%)	456 (67·5%)	477 (72·1%)	459 (69·8%)	466 (69·4%)	299 (66·6%)
Weight (kg)	78·9 (18·0)	79·2 (17·1)	78·7 (15·5)	78·6 (16·0)	79·3 (15·4)	78·2 (15·4)
Creatinine clearance (mL/min)	103·1 (43·9)	94·6 (37·5)	94·4 (34·4)	93·5 (35·5)	95·2 (34·8)	95·0 (33·9)
Creatinine clearance <50 mL/min	9 (7·7%)	56 (8·9%)	46 (7·5%)	50 (8·1%)	51 (8·2%)	34 (8·1%)
Medical history						
Hypertension	85 (69·1%)	465 (69·7%)	457 (70·7%)	467 (72·2%)	466 (70·8%)	297 (67·2%)
Dyslipidaemia requiring therapy	56 (45·5%)	341 (51·1%)	318 (49·2%)	320 (49·5%)	327 (49·7%)	217 (49·1%)
Current smoker	40 (32·5%)	212 (31·8%)	200 (31·0%)	208 (32·1%)	209 (31·8%)	152 (34·4%)
Diabetes mellitus	31 (25·2%)	190 (28·5%)	177 (27·4%)	201 (31·1%)	189 (28·7%)	125 (28·3%)
Previous myocardial infarction	22 (17·9%)	123 (18·4%)	132 (20·4%)	169 (26·1%)	146 (22·2%)	90 (20·4%)
Index presentation						
ST deviation ≥0·1 mV	61 (48·8%)	366 (54·1%)	389 (58·8%)	367 (55·8%)	394 (58·7%)	254 (56·6%)
Elevated troponin or CK MB	106 (84·8%)	508 (75·1%)	509 (76·9%)	518 (78·7%)	508 (75·7%)	353 (78·6%)

Data are mean (SD) or number (%). ST deviation includes depression or transient elevation. Percentages based on available data for every variable. UFH=unfractionated heparin. CK=creatine kinase.

Table 1: **Baseline characteristics**

	Otamixaban (mg/kg/h)					UFH+eptifibatide (n=449)
	0·035 (n=125)	0·070 (n=676)	0·105 (n=662)	0·140 (n=658)	0·175 (n=671)	
Study drug duration (h)						
Drug A (otamixaban or placebo)	5·42 (3·40–21·17)	5·17 (3·55–18·58)	5·40 (3·50–18·58)	4·92 (3·38–19·83)	5·08 (3·55–17·63)	4·87 (3·58–19·10)
Drug B (UFH or placebo)	5·38 (3·33–20·52)	5·15 (3·52–18·63)	5·37 (3·42–18·48)	4·88 (3·37–19·00)	5·00 (3·50–17·50)	4·85 (3·53–19·00)
Drug C (eptifibatide or placebo)	21·22 (10·70–27·75)	21·47 (7·02–26·48)	20·97 (8·67–25·75)	21·30 (8·33–25·95)	20·75 (8·00–24·67)	20·48 (8·32–25·17)
Other drugs						
Aspirin	122 (97·6%)	667 (98·7%)	651 (98·3%)	649 (98·6%)	657 (97·9%)	443 (98·7%)
Clopidogrel	123 (98·4%)	668 (98·8%)	651 (98·3%)	645 (98·0%)	664 (99·0%)	441 (98·2%)
Clopidogrel ≥600 mg	31 (24·8%)	130 (19·2%)	126 (19·0%)	128 (19·5%)	137 (20·4%)	88 (19·6%)
Clopidogrel before angiography*	114 (92·7%)	635 (94·6%)	614 (93·5%)	613 (94·9%)	628 (95·6%)	424 (95·9%)
Time from clopidogrel loading to angiography (h)	18·19 (7·17–24·88)	17·67 (6·42–24·70)	17·58 (6·03–25·20)	17·50 (5·83–24·92)	17·98 (5·70–24·33)	18·17 (5·83–24·77)
Anticoagulant before randomisation†	85 (68·0%)	425 (62·9%)	443 (66·9%)	415 (63·1%)	446 (66·5%)	297 (66·1%)
UFH (bolus or infusion)	41 (32·8%)	225 (33·3%)	216 (32·6%)	219 (33·3%)	240 (35·8%)	157 (35·0%)
Low-molecular-weight heparin	49 (39·2%)	215 (31·8%)	255 (38·5%)	220 (33·4%)	234 (34·9%)	153 (34·1%)
β blocker	96 (77·4%)	545 (80·7%)	561 (85·0%)	548 (83·5%)	554 (82·8%)	380 (84·6%)
Statin	107 (86·3%)	590 (87·4%)	586 (88·8%)	573 (87·3%)	573 (85·7%)	395 (88·0%)
Procedures						
Angiography	123 (98·4%)	671 (99·3%)	657 (99·2%)	646 (98·2%)	657 (97·9%)	442 (98·4%)
Day 1	78 (63·4%)	448 (66·7%)	433 (65·9%)	423 (65·4%)	456 (69·3%)	295 (66·6%)
Day 2	43 (35·0%)	192 (28·7%)	184 (28·0%)	182 (28·2%)	172 (26·3%)	127 (28·9%)
Day 3 or 4	2 (1·6%)	31 (4·6%)	40 (6·1%)	41 (6·4%)	29 (4·4%)	20 (4·5%)
Time from randomisation to angiography (h)	5·82 (4·25–19·25)	5·20 (3·75–17·15)	5·30 (3·60–17·95)	4·93 (3·65–18·62)	5·20 (3·65–16·15)	5·15 (3·82–17·77)
PCI	81 (64·8%)	417 (61·7%)	419 (63·3%)	396 (60·2%)	433 (64·5%)	286 (63·7%)
Stent‡	70 (86·4%)	399 (95·7%)	393 (93·8%)	373 (94·2%)	407 (94·0%)	263 (92·0%)
CABG without previous PCI	5 (4·0%)	20 (3·0%)	27 (4·1%)	26 (4·0%)	16 (2·4%)	23 (5·1%)

Data are median (IQR) and number (%). Percentages based on available data for every variable. UFH=unfractionated heparin. PCI=percutaneous coronary intervention. CABG=coronary-artery bypass grafting. *Percentage of patients who underwent angiography. †Patients could have received more than one type of anticoagulant before study drug. ‡Percentage of patients who underwent PCI.

Table 2: **Study drug, cardiac drugs, and procedures**

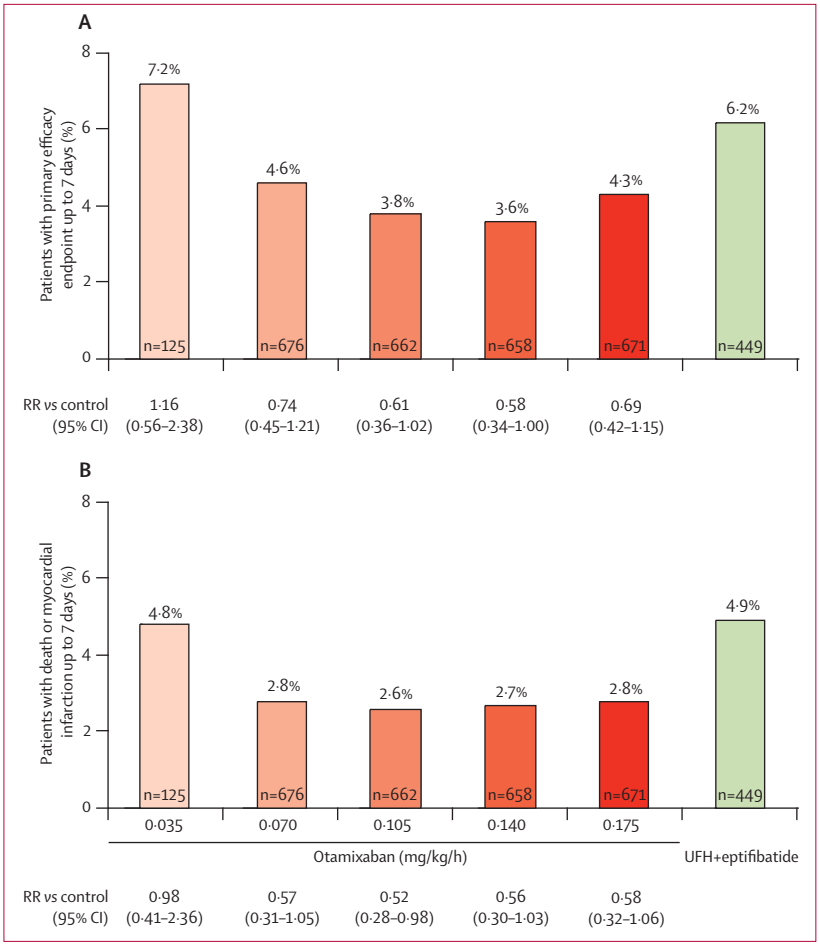

Figure 2: **Efficacy outcomes up to 7 days**
(A) Proportion of patients with the primary efficacy endpoint of all-cause death, myocardial infarction, severe recurrent myocardial ischaemia requiring urgent revascularisation, or bailout use of a glycoprotein IIb/IIIa inhibitor for recurrent ischaemia or for a thrombotic complication during percutaneous coronary intervention. p=0·34 for trend across the otamixaban dose group. Relative risks (RR) and 95% CIs compared with the control group of unfractionated heparin (UFH) plus eptifibatide are displayed below the corresponding bars in the graph. The RR for otamixaban doses 0·105 and 0·140 mg/kg/h combined versus unfractionated heparin plus eptifibatide was 0·60, 95% CI 0·38–0·94; p=0·0236. (B) Proportion of patients with all-cause death or myocardial infarction. The RR for otamixaban doses 0·105 and 0·140 mg/kg/h combined versus unfractionated heparin plus eptifibatide was 0·54, 95% CI 0·32–0·91; p=0·0198. The p values represent nominal p values without correction for multiple hypothesis testing.

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12 IU/kg/h [initial maximum 1000 IU/h]) plus eptifibatide (Schering Corp, Kenilworth, USA) (180 μg/kg intravenous bolus [maximum 22·6 mg] followed by an infusion of 2·0 μg/kg/min [maximum 15 mg/h] or 1·0 μg/kg/min in patients with a creatinine clearance <50 mL/min).

An independent statistician generated a randomisation scheme and then provided it to a central randomisation service, which then used dynamic allocation of randomisation blocks to investigational sites. Investigators used a telephone-based interactive voice response system to receive the study treatment kit box number to be dispensed to the patient. Both investigators and patients were unaware of treatment allocation. Study drugs were administered with a triple-dummy design. Investigators monitoring the anticoagulation to adjust the dose of unfractionated heparin to maintain an activated partial thromboplastin time of 1·5–2·0 times control were masked to group assignment.

Procedures

Otamixaban (or matching placebo) and unfractionated heparin (or matching placebo) were to be administered until the end of the percutaneous coronary intervention. Eptifibatide (or matching placebo) was to be administered until 18–24 h after the end of the percutaneous coronary intervention. If no percutaneous coronary intervention was done, study drugs could be discontinued after diagnostic angiography or continued as long as clinically indicated up until day 4 of admission to hospital. Study drug was to be discontinued at least 3 h before coronary-artery bypass grafting. At the discretion of the investigator, a patient could receive bailout glycoprotein IIb/IIIa inhibitor, which was provided as a masked bolus of eptifibatide (or matching placebo for patients already on eptifibatide), to be followed by an infusion of open-label eptifibatide (webappendix p 1).

Background treatment was at the discretion of the investigator. The protocol recommended that participants receive aspirin and clopidogrel according to practice guidelines at randomisation (if not already administered) and that both drugs be continued for the duration of the study. Anticoagulants started before enrolment were discontinued, and study drugs were begun either 90–150 min after discontinuation of an unfractionated heparin infusion or 8–12 h after the last dose of low-molecular-weight heparin. Patients were to be managed with an early invasive strategy with angiography within 72 h of randomisation and subsequent coronary revascularisation as indicated.

Patients were followed up for clinical endpoints and adverse outcomes up to 180 days (or 90 days after the last patient was randomly assigned, whichever came first). An independent Data Monitoring Committee reviewed unblinded data for patient safety; no interim analyses for efficacy or futility were done. During the trial, this committee recommended that the group receiving the lowest dose of otamixaban (0·035 mg/kg/h) be discontinued because of clinical evidence of inadequate anticoagulation. The protocol was immediately amended in accordance with that recommendation, and participants were subsequently randomly assigned in 2:2:2:2:1 ratio to the remaining otamixaban and control groups, respectively.

Outcomes

The primary efficacy endpoint was a composite of all-cause death, myocardial infarction, severe recurrent myocardial ischaemia requiring urgent revascularisation, or bailout use of a glycoprotein IIb/IIIa inhibitor for recurrent ischaemia or for a thrombotic complication during percutaneous coronary intervention up to 7 days. Other efficacy endpoints were individual components of the composite endpoint up to 7 days, the composite endpoint

up to 180 days, and procedural thrombotic complications (including abrupt vessel or side-branch closure; new intracoronary, catheter, or guidewire thrombus; distal embolisation; or no or slow reflow). The primary safety endpoint was TIMI major or minor bleeding not related to coronary-artery bypass grafting up to 7 days. Other safety endpoints included all TIMI major bleeding, TIMI minor bleeding, TIMI minimal bleeding, transfusion, and stroke.[9] A clinical events committee reviewed and adjudicated all deaths, suspected myocardial ischaemic events, strokes, bailout use of a glycoprotein IIb/IIIa inhibitor, procedural thrombotic complications, and suspected bleeding events.

Statistical analysis

Baseline characteristics are presented as means with SDs, medians with IQRs, or counts and percentages as appropriate for the variable. The incidence of the primary efficacy and safety endpoints were calculated for every group. To test for a trend across otamixaban regimens, we used a Cochran-Armitage test. To compare otamixaban regimens with the control group of unfractionated heparin plus eptifibatide, relative risks (RRs) were calculated with 95% CIs. Event rates up to 180 days were estimated with the Kaplan-Meier method. Efficacy analyses were done in the intention-to-treat population; safety analyses were done in the treated population. The initial sample size of 450 participants per group was planned to provide 80% power at a two-sided α of 0·05 to detect a trend across the five dose groups of otamixaban, resulting in a primary endpoint event rate ranging from 8% in the lowest otamixaban dose group to 4% in the highest. After premature discontinuation of the lowest dose group, the sample size was reassessed and we determined that 680 participants in the remaining otamixaban dose groups were needed to maintain 80% power across the five otamixaban dose groups.

This study is registered with ClinicalTrials.gov, number NCT00317395.

Role of the funding source

The study was designed collaboratively by the TIMI Study Group, the sponsors, and a steering committee of investigators. All analyses were done by the TIMI Study Group with an independent copy of the complete database. MSS, EMA, and EB wrote all drafts of the report and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile of the 3241 patients who were randomly assigned. Table 1 summarises the baseline characteristics, which were similar between the treatment groups. Use of guideline-recommended cardiac drugs was high (table 2), including 3192 (98%) patients receiving clopidogrel and 3028 of the patients undergoing angiography (95%) receiving it upstream before angiography. In accordance with the protocol recommendation, 3196 (99%) patients underwent coronary angiography, and 2133 of those (67%) did so on the day of randomisation (table 2). Vascular access was obtained through the femoral approach in 2518 patients (79%), the radial approach in 662 (21%), and the brachial approach in 16 (1%). 2032 (63%) patients underwent percutaneous coronary intervention and 117 (4%) underwent coronary-artery bypass grafting (table 2). The median duration of treatment with otamixaban or unfractionated heparin was roughly 5 h and with eptifibatide or placebo was 21 h (table 2).

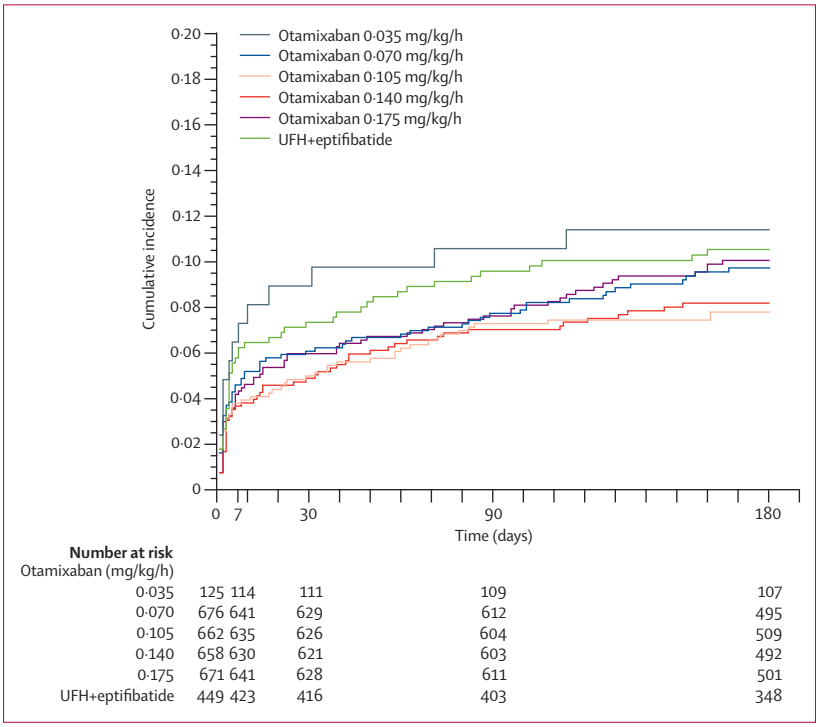

***Figure 3*: Primary efficacy outcome up to 180 days**

Kaplan-Meier estimates of the cumulative incidence of the primary efficacy endpoint of all-cause death, myocardial infarction, severe recurrent myocardial ischaemia requiring urgent revascularisation, or bailout use of a glycoprotein IIb/IIIa inhibitor for recurrent ischaemia or for a thrombotic complication during percutaneous coronary intervention. UFH=unfractionated heparin.

Figure 2A shows the rates of the primary efficacy endpoint—the composite of all-cause death, myocardial infarction, severe recurrent myocardial ischaemia requiring urgent revascularisation, or bailout use of a glycoprotein IIb/IIIa inhibitor—up to 7 days across the treatment groups. There was no statistically significant trend in the rate of the primary efficacy endpoint across the otamixaban groups (p=0·34). However, in all the otamixaban groups apart from the lowest dose, the point estimate for the primary efficacy endpoint favoured otamixaban over unfractionated heparin plus eptifibatide (figure 2A). Specifically, at intermediate doses (0·105 and 0·140 mg/kg/h), treatment with otamixaban resulted in about 40% reductions in the primary efficacy endpoint (figure 2A). These differences in the composite endpoint were driven by reductions of 45% or more in death or

	Otamixaban (mg/kg/h)					UFH+eptifibatide (n=449)
	0·035 (n=125)	0·070 (n=676)	0·105 (n=662)	0·140 (n=658)	0·175 (n=671)	
Primary efficacy endpoint	9 (7·2%)	31 (4·6%)	25 (3·8%)	24 (3·6%)	29 (4·3%)	28 (6·2%)
Death, MI, or urgent revascularisation	7 (5·6%)	19 (2·8%)	21 (3·2%)	20 (3·0%)	23 (3·4%)	25 (5·6%)
Death or MI	6 (4·8%)	19 (2·8%)	17 (2·6%)	18 (2·7%)	19 (2·8%)	22 (4·9%)
Death	1 (0·8%)	9 (1·3%)	8 (1·2%)	8 (1·2%)	8 (1·2%)	8 (1·8%)
MI*	5 (4·0%)	11 (1·6%)	9 (1·4%)	13 (2·0%)	12 (1·8%)	14 (3·1%)
Spontaneous	3 (2·4%)	5 (0·7%)	6 (0·9%)	6 (0·9%)	6 (0·9%)	6 (1·3%)
Peri-PCI	3 (2·4%)	4 (0·6%)	3 (0·5%)	6 (0·9%)	5 (0·8%)	7 (1·6%)
Urgent revascularisation	1 (0·8%)	2 (0·3%)	5 (0·8%)	2 (0·3%)	4 (0·6%)	3 (0·7%)
Protocol-defined bailout GP IIb/IIIa inhibitor use	4 (3·2%)	15 (2·2%)	9 (1·4%)	5 (0·8%)	8 (1·2%)	5 (1·1%)

Data are number (%) of patients. UFH=unfractionated heparin. MI=myocardial infarction. PCI=percutaneous coronary intervention. GP=glycoprotein. *Patients could have had both a spontaneous and a peri-PCI myocardial infarction.

Table 3: **Efficacy outcomes up to 7 days**

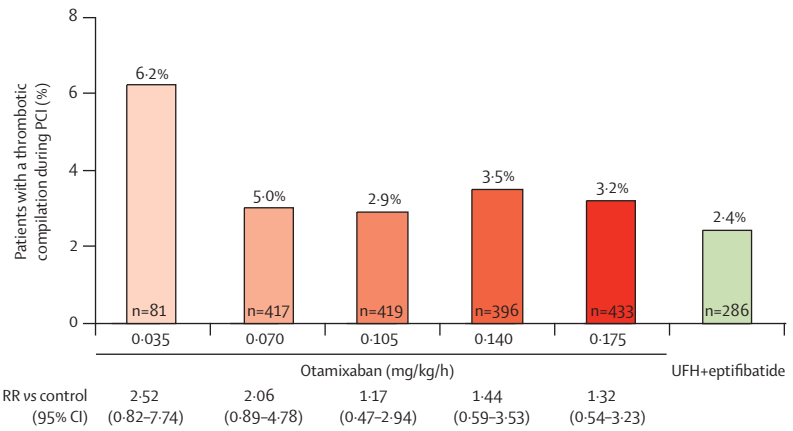

Figure 4: **Thrombotic complication during percutaneous coronary intervention (PCI)**
Relative risks (RR) and 95% CI compared with the control group of unfractionated heparin (UFH) plus eptifibatide are displayed below the corresponding bars in the graph. The RR for otamixaban doses 0·035 and 0·070 mg/kg/h combined versus unfractionated heparin plus eptifibatide was 2·13, 95% CI 0·94–4·85; p=0·0627.

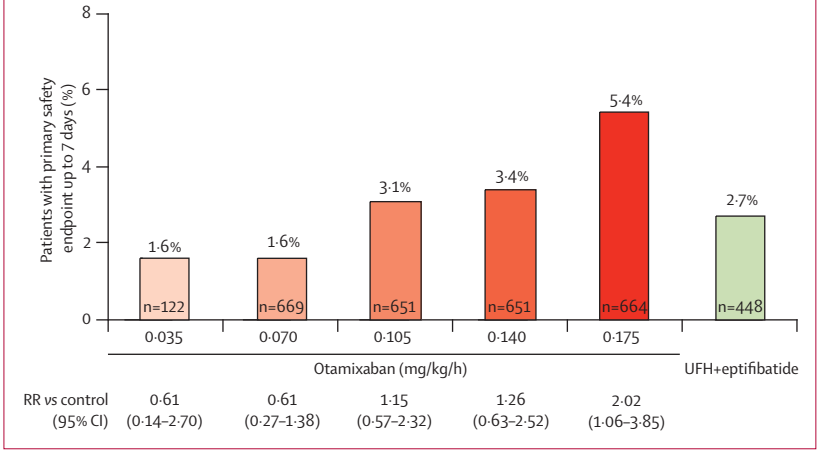

Figure 5: **TIMI major or minor bleeding not related to coronary-artery bypass grafting up to 7 days**
Relative risks (RR) and 95% CIs compared with the control group of unfractionated heparin (UFH) plus eptifibatide are displayed below the corresponding bars in the graph. The RR for otamixaban doses 0·105 and 0·140 mg/kg/h combined versus unfractionated heparin plus eptifibatide was 1·20, 95% CI 0·64–2·27; p=0·56.

myocardial infarction compared with unfractionated heparin plus eptifibatide at these doses (figure 2B). The differences in the rates of the primary endpoint seen by 7 days persisted during 180 days of follow-up (figure 3).

Table 3 shows the rates of individual efficacy endpoints up to 7 days. Of note, patients given low doses of otamixaban (0·035 and 0·070 mg/kg/h) tended to have two-fold to three-fold higher rates of bailout glycoprotein IIb/IIIa inhibitor use for recurrent ischaemia or for a thrombotic complication than did those given unfractionated heparin plus eptifibatide (RR 2·87, 95% CI 0·78–10·54 for otamixaban 0·035 mg/kg/h; RR 1·99, 0·73–5·44 for otamixaban 0·070 mg/kg/h; RR 2·13, 0·80–5·47, p=0·12 for doses combined). Patients given otamixaban at doses greater than 0·105 mg/kg/h had rates of bailout glycoprotein IIb/IIIa inhibitor use similar to that noted with unfractionated heparin plus eptifibatide (table 3).

In patients who underwent percutaneous coronary intervention, TIMI flow grade 3 and procedural success (defined as a residual stenosis <50% and TIMI flow grade 3) were each achieved in more than 90% of cases across all treatment groups (data not shown). Patients given low doses of otamixaban (0·035 and 0·070 mg/kg/h) tended to have two-fold to three-fold higher rates of procedural thrombotic complications than did those given unfractionated heparin plus eptifibatide (figure 4). Patients given otamixaban at doses greater than 0·105 mg/kg/h had rates of thrombotic complications similar to those noted with unfractionated heparin plus eptifibatide (figure 4; webappendix p 2 provides further details).

Figure 5 shows the rates of the primary safety endpoint, TIMI major or minor bleeding not related to coronary-artery bypass grafting, up to 7 days across the treatment groups. We noted a significant dose response across the five otamixaban groups (p=0·0001 for trend). Patients given low doses of otamixaban (0·035 and 0·070 mg/kg/h) tended to have lower rates of the primary safety endpoint, those given intermediate doses (0·105 and 0·140 mg/kg/h) had similar rates, and those

given the highest dose (0·175 mg/kg/h) had a significantly higher rate (p=0·0273) than did those given unfractionated heparin plus eptifibatide (figure 5). The webappendix p 3 shows the rate of the net clinical outcome (the composite of the primary efficacy and the primary safety endpoint) up to 7 days across the treatment groups.

Table 4 shows the rates of additional safety endpoints up to 7 days. Compared with patients given unfractionated heparin plus eptifibatide, patients given low doses of otamixaban (0·035 and 0·070 mg/kg/h) had similar rates of minimal bleeding, those given intermediate doses (0·105 and 0·140 mg/kg/h) had two-fold increases in minimal bleeding (RR 1·95, 95% CI 1·26–3·03, and 2·12, 1·37–3·27, respectively), and those given the highest dose (0·175 mg/kg/h) had a nearly a three-fold increase in minimal bleeding (RR 2·83, 1·86–4·31). Safety outcomes up to 30 days paralleled the data up to 7 days (webappendix p 4).

Discussion

The SEPIA-ACS1 TIMI 42 trial examined the efficacy and safety of anticoagulation with otamixaban—a novel, intravenous, direct, selective inhibitor of factor Xa—in patients with high-risk non-ST-elevation acute coronary syndromes. Treatment with otamixaban at doses of 0·105 or 0·140 mg/kg/h was associated with a 40% reduction in death or ischaemic complications compared with unfractionated heparin plus eptifibatide. Doses of otamixaban of 0·070 mg/kg/h or less were associated with increases towards at least a doubling in the need for a bailout glycoprotein IIb/IIIa inhibitor and in thrombotic complications during percutaneous coronary intervention, and thus seem to offer inadequate anticoagulation. Conversely, otamixaban 0·175 mg/kg/h resulted in significantly more TIMI major or minor bleeding than did unfractionated heparin plus eptifibatide. Otamixaban doses of 0·105 and 0·140 mg/kg/h were associated with non-significant excesses of TIMI major and TIMI major or minor bleeding compared with unfractionated heparin plus eptifibatide. Thus otamixaban given with a bolus of 0·080 mg/kg followed by an infusion of 0·100–0·140 mg/kg/h seems to be the most reasonable choice for future study.

Otamixaban has several attractive pharmacological properties. Its selective inhibition of factor Xa enables it to inhibit thrombin generation rather than thrombin activity.[6] In animal models of thrombosis, brief infusions of otamixaban resulted in long-term arterial patency, which was better than that achieved with unfractionated heparin.[10] This finding accords with our observation of a tendency toward lower ischaemic events with otamixaban than with unfractionated heparin plus eptifibatide, despite fairly brief durations of therapy. As a small, direct inhibitor of factor Xa, otamixaban can inhibit both fluid-phase and clot-bound factor Xa.[6] Otamixaban is reversible, with near immediate onset of action after a bolus and an initial half-life of 30 min,[11] offering rapid on–off anticoagulant activity, which is a desirable feature in the setting of invasive management of an acute coronary syndrome. Otamixaban is mainly cleared unchanged via the biliary system with less than 25% renal excretion, suggesting no need for dose modification in case of renal insufficiency.[11] Similar to some other anti-Xa drugs, otamixaban can prolong the activated partial thromboplastin time (aPTT). However, monitoring of aPTT is not necessary since there is a very strong correlation between otamixaban's anti-Xa pharmacodynamic effect and its blood concentration, and only small variability between patients in blood concentration for a specific dose.[12]

The results of SEPIA-ACS1 TIMI 42 are consistent with those of the earlier SEPIA-PCI trial[8] in patients undergoing elective percutaneous coronary intervention. In that study, otamixaban doses in the range of 0·120–0·160 mg/kg/h were associated with 30–55% lower rates of death or ischaemic complications and similar rates of TIMI major or minor bleeding compared with unfractionated heparin.[8]

We compared otamixaban with unfractionated heparin plus eptifibatide on a recommended background of dual antiplatelet therapy with aspirin plus clopidogrel. Not

	Otamixaban (mg/kg/h)					UFH+eptifibatide (n=448)
	0·035 (n=122)	0·070 (n=669)	0·105 (n=651)	0·140 (n=651)	0·175 (n=664)	
TIMI major or minor bleeding not related to CABG*	2 (1·6%)	11 (1·6%)	20 (3·1%)	22 (3·4%)	36 (5·4%)	12 (2·7%)
At vascular access site	1 (0·8%)	6 (0·9%)	7 (1·1%)	15 (2·3%)	18 (2·7%)	6 (1·3%)
Not at vascular access site	1 (0·8%)	5 (0·7%)	14 (2·2%)	9 (1·4%)	19 (2·9%)	6 (1·3%)
TIMI major bleeding not related to CABG	1 (0·8%)	5 (0·7%)	9 (1·4%)	8 (1·2%)	11 (1·7%)	3 (0·7%)
TIMI major bleeding	1 (0·8%)	12 (1·8%)	22 (3·4%)	17 (2·6%)	23 (3·5%)	8 (1·8%)
TIMI minor bleeding	1 (0·8%)	6 (0·9%)	11 (1·7%)	14 (2·2%)	25 (3·8%)	9 (2·0%)
Transfusion	8 (6·6%)	41 (6·1%)	40 (6·1%)	50 (7·7%)	55 (8·3%)	41 (9·2%)
TIMI minimal bleeding	5 (4·1%)	45 (6·7%)	71 (10·9%)	77 (11·8%)	105 (15·8%)	25 (5·6%)
Stroke	0 (0·0%)	1 (0·1%)	3 (0·5%)	1 (0·2%)	3 (0·5%)	1 (0·2%)

Data are number (%) of patients. UFH=unfractionated heparin. CABG=coronary-artery bypass grafting. *Patients could have had both a vascular and non-vascular access site bleed.

Table 4: **Safety outcomes up to 7 days**

only is unfractionated heparin one of the most commonly used anticoagulants in non-ST-elevation acute coronary syndromes, but in the setting of an early invasive strategy, it has been given a class I recommendation by the European Society of Cardiology, the American College of Cardiology, and the American Heart Association.[4,13] Similarly, these professional societies give a class IIa recommendation for the addition of a small-molecule glycoprotein IIb/IIIa inhibitor such as eptifibatide to upstream dual oral antiplatelet therapy in high-risk patients. Thus, our control group represents therapy for high-risk patients with non-ST-elevation acute coronary syndromes that has been endorsed by guidelines from professional societies and approved by regulatory agencies. Moreover, the rates of ischaemic and bleeding events in our control group are similar to those recorded in patients given similar regimens in other large trials.[14]

However, several alternative anticoagulants have been studied in non-ST-elevation acute coronary syndromes. The low-molecular-weight heparin enoxaparin has better efficacy than does unfractionated heparin,[15] but the two drugs seem to be fairly similar in the setting of an early invasive strategy.[16,17] Treatment with the direct thrombin inhibitor bivalirudin, when compared with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor, resulted in similar rates of ischaemic events and lower rates of bleeding,[14] the opposite of what we recorded with intermediate doses of otamixaban in this study. Fondaparinux is an indirect factor Xa inhibitor and is not shortacting (half-life of 17–21 h). When compared with enoxaparin, it resulted in similar short-term rates of ischaemic events, less bleeding, and lower 30-day mortality.[18] However, use of fondaparinux was associated with a high rate of catheter-related thromboses, and supplementation with another anticoagulant is needed when percutaneous coronary intervention is required.[19] In SEPIA-ACS1 TIMI 42, we noted no catheter-related thromboses with either the 0·105 or the 0·140 mg/kg/h otamixaban doses. Nonetheless, careful tracking of these events will be needed in a phase 3 trial. Of note, neither bivalirudin nor fondaparinux has yet been approved in the USA for the treatment of non-ST-elevation acute coronary syndromes.

Several oral factor Xa inhibitors are being assessed for long-term outpatient use after clinical stabilisation from an acute coronary syndrome. Both rivaroxaban and apixaban have been studied in phase 2 trials and have shown promising reductions in ischaemic events and dose-dependent increases in bleeding.[20,21] Thus, patients could receive intense intravenous factor Xa inhibition during admission for their acute coronary syndrome, and then transition to long-term oral factor Xa inhibition.

Increased potency oral antiplatelet agents such as prasugrel and ticagrelor are emerging.[22–24] As these agents are adopted into clinical practice, the efficacy and safety profile of otamixaban will need to be assessed in combination with them. Moreover, the need for and optimum timing of glycoprotein IIb/IIIa inhibition remains debated,[25,26] and will also need to be reassessed in the context of new oral antiplatelet agents with increased potency.

Our study offers additional preliminary evidence for the efficacy and safety of direct factor Xa inhibition with otamixaban in patients with coronary disease. Examination of the ischaemic, thrombotic, and bleeding event rates across the five doses tested provides a clear signal as to the optimum dose to be used in a large phase 3 trial of otamixaban in acute coronary syndromes.

Contributors

MSS, EMA, CHM, and EB conceived and designed the research. PW, IOE, RGK, AS, and RP acquired the data. MSS, EMA, CFC, CHM, and EB analysed and interpreted the data. CFC did statistical analyses. MSS drafted the initial report. EMA, CHM, and EB participated in funding and supervision. MSS, EMA, PW, IOE, RGK, AS, RP, and EB made critical revision of the report for important intellectual content. All authors approved the final version of the report.

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Conflicts of interest

The TIMI Study Group receives research grant support from Sanofi-Aventis, Johnson & Johnson, Bayer Healthcare AG, and Daiichi Sankyo. Additionally, MSS reports receiving honoraria and consultant fees from Sanofi-Aventis and honoraria from Bristol-Myers Squibb. EMA reports receiving research grants from Sanofi-Aventis and Daaichi-Sankyo. RGK reports receiving honoraria from Sanofi-Aventis and Bayer AG. EB reports receiving grant support from Johnson & Johnson and honoraria and consultant fees from Sanofi-Aventis. All other authors declare that they have no conflicts of interest.

Acknowledgments

This study was funded by Sanofi-Aventis.

References

1 Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med* 2008; **359:** 938–49.

2 Andersen H, Greenberg DL, Fujikawa K, Xu W, Chung DW, Davie EW. Protease-activated receptor 1 is the primary mediator of thrombin-stimulated platelet procoagulant activity. *Proc Natl Acad Sci USA* 1999; **96:** 11189–93.

3 Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. *JAMA* 1996; **276:** 811–15.

4 Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007; **116:** e148–304.

5 Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126** (suppl)**:** 188S–203S.

6 Chu V, Brown K, Colussi D, et al. Pharmacological characterization of a novel factor Xa inhibitor, FXV673. *Thromb Res* 2001; **103:** 309–24.

7 Rebello SS, Bentley RG, Morgan SR, et al. Antithrombotic efficacy of a novel factor Xa inhibitor, FXV673, in a canine model of coronary artery thrombolysis. *Br J Pharmacol* 2001; **133:** 1190–98.

8 Cohen M, Bhatt DL, Alexander JH, et al. Randomized, double-blind, dose-ranging study of otamixaban, a novel, parenteral, short-acting direct factor Xa inhibitor, in percutaneous coronary intervention: the SEPIA-PCI trial. *Circulation* 2007; **115:** 2642–51.

9 Sabatine MS, McCabe CH, Gibson CM, Cannon CP. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)—Thrombolysis in Myocardial Infarction (TIMI) 28 trial. *Am Heart J* 2005; **149:** 227–33.

10 Rebello SS, Kasiewski CJ, Wang W, et al. Role of short-term inhibition of factor Xa by FXV673 in arterial passivation: a study in a chronic model of thrombosis in conscious dogs. *J Cardiovasc Pharmacol* 2001; **38:** 288–97.

11 Paccaly A, Frick A, Rohatagi S, et al. Pharmacokinetics of otamixaban, a direct factor Xa inhibitor, in healthy male subjects: pharmacokinetic model development for phase 2/3 simulation of exposure. *J Clin Pharmacol* 2006; **46:** 37–44.

12 Hinder M, Frick A, Jordaan P, et al. Direct and rapid inhibition of factor Xa by otamixaban: a pharmacokinetic and pharmacodynamic investigation in patients with coronary artery disease. *Clin Pharmacol Ther* 2006; **80:** 691–702.

13 Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J* 2007; **28:** 1598–660.

14 Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.

15 Antman EM, Cohen M, Radley D, et al, for the TIMI 11B (Thrombolysis in Myocardial Infarction) and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) Investigators. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999; **100:** 1602–08.

16 Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 2004; **292:** 45–54.

17 Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA* 2004; **292:** 55–64.

18 Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 1464–76.

19 Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007; **50:** 1742–51.

20 Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009; **374:** 29–38.

21 Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation* 2009; **119:** 2877–85.

22 Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–15.

23 Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 2007; **50:** 1844–51.

24 James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* 2009; **157:** 599–605.

25 Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. *JAMA* 2007; **297:** 591–602.

26 Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009; **360:** 2176–90.